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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/862,571	05/21/2001	Glenn McGall	AFMX-P02-038	9482

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/862,571	MCGALL ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/02/2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,43 and 44* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,9,12,43,44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

1. Amendment filed 05/02/2005 Is acknowledged. Claims 43,44 are added. Claims 1-12,43,44 are pending. Claims 4,5,8-11 remain withdrawn from consideration. Claims 1-3,6,7,9,12,43,44 are addressed to the extent they read on the elected species.

Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-3,6,7,9,12,43,44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims remain rejected for the reasons of record. It is not clear how use of phosphoroamidate (such as elected species of formula II) will result in formation of phosphate. The claims, as drawn to elected species (of claim 9), are drawn to replacing an oligonucleotide protective group with a negatively charged phosphate group by removing protective group and reacting thus formed active site with a phosphoramidite of formula II.

Phosphate, according to a dictionary definition is a

$(PO_4)^{-3}$ ion, or a compound comprising $(PO_4)^{-3}$

(see, e.g., on-line Webster Dictionary, *http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=phosphate*).

Then, it is not clear how a compound of Formula II, which a) have different valency, and b) do not have negatively charged groups, can introduce $(PO_4)^{-3}$ group as claimed. Note that the method step recites "replacing", not any other type of conversion of the protecting or any other intermediary group. The claims are rejected as failing to set forth the subject matter that applicant regards as their invention. In the response filed 05/02/05, applicant acknowledges that conversion of phosphite to phosphate would require additional steps, such as oxidizing which are essential for the practice of the invention.

Response to arguments

Applicant argues that the claims are definite by virtue of reciting the initial step and the final product. Examiner maintains that neither the claims, nor specification address the missing step of conversion of phosphates into phosphates and all that the instant claims require is addition of phosphoramidate as a terminal group to an unprotected nucleotide. According to MPEP, 2172.01,

> ...a claim which fails to interrelate essential elements of the invention as defined by applicant(s) in the specification or in other statements of record may be rejected under 35 U.S.C. 112, second paragraph, for failure to point out and distinctly claim the invention.

Claim terms are presumed to have the ordinary and customary meanings attributed to them by those of ordinary skill in the art. *Sunrace Roots Enter. Co. v. SRAM Corp.*, 336

F.3d 1298, 1302, 67 USPQ2d 1438, 1441 (Fed. Cir. 2003); *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 67 USPQ2d 1132, 1136 (Fed. Cir. 2003)("In the absence of an express intent to impart a novel meaning to the claim terms, the words are presumed to take on the ordinary and customary meanings attributed to them by those of ordinary skill in the art."). It is the use of the words in the context of the written description and customarily by those skilled in the relevant art that accurately reflects both the "ordinary" and the "customary" meaning of the terms in the claims. *Ferguson Beauregard/Logic Controls v. Mega Systems*, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003). In the instant case, the method step of using phosphoroamidites, in view of description in the specification, means nothing more than forming phosphite group, not phosphate group as asserted by applicant.

Claim Rejections - 35 USC § 112, first paragraph.

3. Claims 1-3,6,7,9,12, 43,44 are rejected under 35 U.S.C. 112, first paragraph, as based on specification which is not enabling. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is maintained for the reasons set forth for claims 1-3,6,7,9,12.

The claims, as drawn to elected species (see claim 9), are drawn to reducing non-specific binding to an oligonucleotide chip by replacing an oligonucleotide protective group with a negatively charged phosphate group by removing protective group and reacting thus formed active site with a phosphoramidite of formula II.

A. First, there is no showing of how to deliver a negatively charged phosphate group by interacting active site with a phosphoramidite of formula II – see rejection under 35 U.S.C. 112, second paragraph above. According to MPEP, 2171.01:

> A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling. *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Such essential matter may include missing elements, steps or necessary structural cooperative relationships of elements described by the applicant(s) as necessary to practice the invention.

B. Second, the specification does not provide support for the claimed effect of reducing non-specific binding by introducing negatively charged phosphate groups. The only example present in specification demonstrates reduction of binding of a specific protein, namely fluorescent protein conjugate phycoeretrin-streptavidin (Example 1[1]). The non-specific background binding does not significantly change with introduction of a phosphate group (compare second and forth rows of Table I, where "m" changes from 0 to 1). The claimed method is supposed to work on arrays testing biological samples. A biological sample is blood, urine, tissue, etc. As any of the molecules present in such sample is capable of binding to the surface of the array, the question is whether specification describes or provides guidance for the claimed universal effect of the negatively charged phosphate residues against non-specific

binding of any of plethora of molecules capable of non-specific binding.. Evidently, biological samples contain plethora of molecules differing both in their chemical activity (i.e., with different affinity to react with phosphate group), and charge (i.e., negatively or positively charged). Thus, any positively charged molecule, e.g. a positively charged protein, would be attracted, rather than repulsed by the negative charge of the phosphate group, the effect that would increase rather than decrease non-specific binding. Specification does not provide any guidance on how to achieve reduction of binding by replacing an oligonucleotide protective group with a negatively charged phosphate group, even less so for the instance wherein phosphate group is introduced by removing protective group and reacting thus formed active site with a phosphoramidite of formula II. Prior art teaches phosphoroamidites as oligonucleotide functionalizing reagents (see, e.g., US Patent 4,914,210) but do not teach that these compounds "reduce non-specific binding of a target molecule".

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Response to arguments

With respect to the first part of rejection, applicant argues that it is known in the art that several reactions can result in formation of phosphate from phosphite group.

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[1] Note that Example 1 does not illustrate the elected embodiment of the method.

This essential method step, however, is not addressed either in specification or in the claims. According to MPEP, 2171.01: "A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling".

With respect to the second aspect of rejection, applicant argues that negative charge of nucleic acids *in vivo* does not cause increase in non-specific binding; otherwise "an organism would not be able to exist". First, the instant method is *in vitro* method, and discussion of "biological samples" in the rejection concerns biological material applied onto the array as claimed. Further, even accepting, *arguendo*, applicant's reasoning, the instant method does not have utility as there is no need to reduce non-specific binding which does not seem to be a problem.

Further, applicant discusses results presented in Tables I and II and asserts that increase in the amount of negative charges improves signal to noise ratio. This argument is not deemed convincing as the point of the rejection is not that increase in the amount of negative charges always fails to reduce no-specific binding (and thus to improve signal to noise ratio). Rather, the point of the rejection is that the breadth of the claims encompasses interaction of the array with any sample, and as any biological sample (e.g., blood, urine, tissue, etc) contains plethora of molecules differing, at least in their charge (i.e., negatively or positively charged), it seems more likely that any positively charged molecule, e.g. a positively charged protein, would be attracted, rather than repulsed by the increase in the negative charge of the array, the effect that would increase rather than decrease non-specific binding. Applicant, in the response, does

not address the issue of the variety of binding molecules of varying nature in the sample; rather, applicant discusses effect of varying surface charge of the array on its interaction with the same sample.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph. D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb